NDA 17-386/S-030

Medeva Americas, Inc.
Attention: Cheryl A. Rini, R.N.
755 Jefferson Road
Rochester, NY 14603-1710

Dear Ms. Rini:

Please refer to your supplemental new drug application dated July 9, 1999, received July 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zaroxolyn (metolazone) Tablets.

We acknowledge receipt of your submission dated July 9, 1999.

This supplemental new drug application provides for final printed labeling revised as follows:

1) Under **PRECAUTIONS: Pediatric Use** subsection has been changed from:

> Safety and effectiveness in pediatric patients have not been established and such use is not recommended.
>
> To:
>
> Safety and effectiveness in pediatric patients have not been established in controlled clinical trials. There is limited experience with the use of ZAROXLYN in pediatric patients with congestive heart failure, hypertension, bronchopulmonary dysplasia, nephrotic syndrome, and nephrogenic diabetes insipidus. Doses used generally ranged from 0.05 to 0.1 mg/kg administered once daily and usually resulted in a 1 to 2.8 kg weight loss and 150 to 300 cc increase in urine output. Not all patients responded and some gained weight. Those patients who did respond did so in the first few days of treatment. Prolonged use (beyond a few days) was generally associated with no further beneficial effect or a return to baseline status and is not recommended.
>
> There is limited experience with the combination of ZAROXLYN and furosemide in pediatric patients with furosemide-resistant edema. Some benefited while others did not or had an exaggerated response with hypovolemia, tachycardia, and orthostatic hypotension requiring fluid replacement. Severe hypokalemia was reported and there was a tendency for diuresis to persist for up to 24 hours after ZAROXLYN was discontinued. Hyperbilirubinemia has been reported in 1 neonate. Close clinical and laboratory monitoring of all children treated with diuretics is indicated. See **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS**.

2) Under HOW SUPPLIED, this section has been changed from:

Store at room temperature. Dispense in a tight, light-resistant container. Keep out of the reach of children.

to:

Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [See USP Controlled Room Temperature]. Protect from light.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted July 16, 1999). Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Edward Fromm
Consumer Safety Officer
301-594-5313.

Sincerely,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research